DRDC Toronto SL 2001-052

ORIGINAL RESERACH

The Impact of Sertraline on Psychomotor Performance

MICHEL A. PAUL, GARY GRAY, AND MARVIN LANGE

PAUL MA, GRAY G, LANGE M. *The impact of sertraline on psychomotor performance.* **Aviat Space Environ Med 2002; 73:964–70.**

Introduction: Aircrew receiving treatment for depression are grounded during treatment and follow-up observation, generally amounting to at least 1 yr. Selective serotonin re-uptake inhibitors (SSRIs) offer new treatment options for depression, of which sertraline (Zoloft ®) has the least imposing side-effect profile. There has been considerable interest in the possibility of returning aircrew to restricted flying duties once stablized on an SSRI with resolution of depression. This study was undertaken to determine whether or not sertraline effects psychomotor performance. ***Method:*** There were 19 volunteer non-depressed subjects (12 men and 7 women) who were assessed for psychomotor performance during placebo and sertraline treatment, in a double-blind cross-over protocol in counter-balanced order. Each treatment arm lasted 5 wk and involved ingesting one capsule each morning. The daily sertraline dose was 50 mg during week 1, 100 mg during week 2, and 150 mg during weeks 3, 4, and 5. Subjects completed a drug side-effect questionnaire and were tested on two psychomotor test batteries once per week, on the same weekday, at the same time of day throughout each 5-wk treatment period. ***Results:*** There was no significant effect of sertraline on serial reaction time, logical reasoning, serial subtraction, or multitask performance. With respect to drug side effects, there was a main effect of drugs on "getting to sleep" ($p < 0.002$), "awakenings" ($p < 0.007$), "returning to sleep" ($p < 0.001$), "dry mouth" ($p < 0.016$), "nausea" ($p < 0.001$), "diarrhea" ($p < 0.026$), "tremors" ($p < 0.005$), and "sweating" ($p < 0.016$), as well as a drug × trials interaction for "drowsiness" ($p < 0.012$), "libido" ($p < 0.039$), and "difficulty with ejaculation" ($p < 0.001$). There was no effect of sertraline on dizziness. ***Conclusions:*** While we found some of the expected side effects due to sertraline, there was no effect on psychomotor performance. These findings support the possibility of selected use in aircrew and should be helpful in the ongoing aeromedical discussion about this evolving issue.

Keywords: antidepressants, aircrew, side effects, psychomotor performance.

CURRENTLY CANADIAN FORCES (CF) aircrew receiving treatment for depression are grounded for the full duration of pharmacologic treatment followed by at least 3 mo observation, often amounting to at least a 1-yr removal from flying duties. Advances in neuroscience research have yielded new treatment options for depression, including selective serotonin reuptake inhibitors (SSRIs). These medications are similar in efficacy to the older tricyclic antidepressants, but their different mechanisms of action results in distinctly different side-effect profiles (2).

The most common side effects associated with tricyclic antidepressants are anticholinergic (dry mouth, constipation, and interference with eye accommodation), cardiovascular (conduction disturbances and hypotension), and weight gain. Further, the anticholinergic activity of this class of drugs appears to be responsible for dose-related cognitive impairment (19). Because of their significant side effect profile, tricyclic antidepressants have been considered unsuitable for use in aircrew while on flying duties.

While serotonin was first identifed in the 1940s because of its vasoconstrictor properties, the neurotransmitter aspects were not realized until some 20 yr after identification. A major step forward in the understanding of serotonin and mental function resulted in the introduction of SSRI antidepressant drugs in the 1980s. The major effect of these drugs is to inhibit the reuptake of serotonin from the neuronal synapses, the net effect of which is to increase serotonin levels in extracellular fluids. Increased synaptic serotonin levels inhibit the firing rates of terminal axons in a feedback inhibition mechanism (17). SSRI drugs have revolutionized psychiatric practice and have been found to be efficacious in a variety of psychiatric disorders (17). Side effects of SSRIs, including cognitive impairment, are generally much less significant than with tricyclic medications (5).

Because of the long period of grounding as well as the perceived stigma associated with treatment for depressive illnesses, aircrew have been extremely reluctant to seek medical attention for symptoms of depression. Further, the clinical observations of most flight surgeons suggest that aircrew, by nature, tend to try to control rather than express affective symptoms including depression. The end result is that aircrew tend not to seek medical attention for even significant depressive illness, with symptoms of difficulty in concentrating, difficulty with decision-making, interference with sleep, and fatigue, all of which constitute potentially significant risks to flight safety. Aircrew tend to "tough it through" depression rather than seek medical help.

From the Defence and Civil Institute of Environmental Medicine, North York, Ontario, Canada.

This manuscript was received for review in April 2001. It was revised in January and May 2002. It was accepted for publication in July 2002.

Address reprint requests to: Michel A. Paul, M.Sc., who is a Defence Scientist, Defence and Civil Institute of Environmental Medicine, 1133 Sheppard Ave. West, P.O. Box 2000, North York, Ontario, Canada M3M 3B9; paul@dicem.dnd.ca

Reprint & Copyright © by Aerospace Medical Association, Alexandria, VA.

104-05734/

Because of the improved side-effect profile of SSRIs and related medications, there has been increasing interest among aeromedical physicians and psychiatrists in defining the conditions under which aircrew might be returned to limited flying duties while taking maintenance doses of these medications after full resolution of depressive illness. Symptoms of depression often remit within weeks of initiating treatment, while a full therapeutic course of antidepressant medication is often 9 mo or longer. The current policy is to keep aircrew grounded for the entire period of treatment, and then for 3 mo afterwards. This prolonged period of grounding has made aircrew reluctant to come forward for treatment except under the most dire circumstances.

These concerns were discussed at a Canadian Forces aeromedical seminar, the result of which was a recommendation to develop guidelines for the use of SSRIs in aircrew maintained on flying duties. Sertraline (marketed as Zoloft®, Pfizer), has fewer reported sedative side effects than many SSRIs, and hence was chosen as being favorable for potential use in aircrew.

A further recommendation of the seminar was that a study be conducted to evaluate the possible impact of sertraline on psychomotor performance from an aeromedical perspective.

Studies evaluating sertraline have consistently shown slight improvements in cognitive function (2). Hindmarch and Bhatti, found improvements in choice reaction time and critical flicker fusion threshold which were inconsistent with subjective reports of drowsiness (6) of 10 healthy female subjects ranging from 25 to 45 yr of age and found sertraline-induced improvements in choice reaction time and critical flicker fusion threshold of 21 elderly healthy volunteers ranging from 60 to 75 yr of age (8). Using 12 healthy non-depressed subjects (6 men and 6 women), Mattila et al. found that sertraline improved critical flicker fusion threshold and did not cause any changes in tracking error, choice reaction time, or digit symbol substitution, in spite of subjective reports of drowsiness (13). CFFT "stands out as unique in reliability as an overall measure of the level of activation of the brain and central nervous system" (6), suggesting that because sertraline raises CFFT, it should not impact on psychomotor performance. A study on depressed subjects (7) showed a small but statistically significant increase in reaction time (21.4 ms) in response to abrupt discontinuation of sertraline treatment. This small increase in reaction time was reversed on reinstatement of treatment, suggesting that sertraline may facilitate "psychomotor speed" via its ability to increase circulating levels of neurotransmitters.

The SSRIs have been associated with case reports of akathisia (restlessness, pacing, purposeless leg and foot movement) which resolves on the discontinuation of the medication. The theoretical cause of this akathisia is due to serotonergic inhibition of dopaminergic neurons in the ventral tegmental area (12).

The SSRIs fluoxetine, paroxetine, and sertraline all delay onset of REM sleep; however, they differ in their impact on SWS (Slow Wave Sleep) and sleep continuity (2). In contrast to fluoxetine and paroxetine, sertraline was associated with a minimal increase in sleep efficiency and reductions in wakefulness during sleep (22). Certainly, sleep disruption, if severe enough, has the potential to impact on psychomotor performance. In acute studies in non-depressed subjects, mood, as assessed by the Profile of Moods Scale (POMS) questionnaire is not affected by either a 100 or 200 mg dose of sertraline (23).

The present protocol was designed to evaluate the impact of sertraline on psychomotor performance of normal healthy subjects from an aeromedical perspective by use of traditional iterative psychomotor testing and a recently developed multitask which simulates the information processing characteristics of flight. While psychomotor performance considerations due to sertraline are a concern with respect to returning aircrew on this medication to flying duties, another aeromedical concern relates to the depressive illness itself, which is not addressed in this paper.

METHODS

The study protocol was approved by the DCIEM Human Ethics Committee. There were 20 volunteer non-depressed healthy subjects (13 men and 7 women) between 22 and 51 yr of age who passed a medical screening, provided written informed consent, and were studied in a double-blind repeated-measures design in which subjects received sertraline and placebo in counterbalanced order. One male subject withdrew from the study because of difficulties with insomnia while taking sertraline. The medications (placebo and sertraline) were prepared by a contract pharmacy in identical capsules for blinding purposes. Each study arm (placebo and sertraline) lasted 5 wk. The medications were taken in single daily morning doses with food in order to mitigate side effects. For the first week, the subjects taking sertraline received a single daily 50 mg dose, which was increased to a daily 100 mg dose during the second week, and increased again to a daily 150 mg dose from week 3 to week 5 inclusive. The subjects were evaluated for psychomotor performance once each week at the end of a week of dosing by performing one trial of each task, on the same weekday, at the same time of day throughout each 5-wk treatment period. At the beginning of each psychomotor test session the subjects were asked to provide their subjective estimates of sleepiness (Stanford Sleepiness Scale) (9) as well as mental and physical fatigue levels (3). The first 5-wk treatment session was followed by a 2-wk drug-free washout period prior to commencement of the second 5-wk treatment period during which the subjects took the alternate medication and again underwent weekly psychomotor testing similar to the first 5-wk treatment session. Each time the subjects underwent their weekly psychomotor performance session, they were asked to complete a questionnaire soliciting their subjective responses to questions regarding any medication-induced side effects.

Because sertraline could be potentially harmful to a fetus, prior to participation, all female subjects were screened for pregnancy (from a serum sample) and

TABLE I SUBJECTIVE SLEEPINESS AND FATIGUE SCORES ACROSS WEEKS FOR PLACEBO AND SERTRALINE SCORE SCALE RANGED FROM 1 TO 7 WITH HIGHER NUMBERS INDICATING MORE SLEEPINESS/FATIGUE

	Subjective Scores (Mean ± SEM)				
	Week 1	Week 2	Week 3	Week 4	Week 5
Sleepiness					
Placebo	2.47 ± 0.20	2.47 ± 0.24	2.23 ± 0.24	2.12 ± 0.21	2.59 ± 0.32
Sertraline	2.37 ± 0.19	2.16 ± 0.22	2.58 ± 0.31	2.56 ± 0.25*	2.22 ± 0.24
Mental fatigue					
Placebo	2.54 ± 0.27	2.38 ± 0.31	2.39 ± 0.30	2.60 ± 0.33	2.65 ± 0.35
Sertraline	2.76 ± 0.32	2.76 ± 0.32	3.16 ± 0.4	2.86 ± 0.34	2.81 ± 0.34
Physical fatigue					
Placebo	2.44 ± 0.29	2.56 ± 0.33	2.67 ± 0.34	2.82 ± 0.36	2.67 ± 0.37
Sertraline	2.90 ± 0.26	2.91 ± 0.31	3.15 ± 0.39	3.01 ± 0.36	3.14 ± 0.39

* Significant difference, $p < 0.05$

were advised to take precautions to avoid pregnancy during this study.

Immediately prior to the study, all subjects were trained to asymptote (best) performance on two psychomotor test batteries. One test battery was a subset of the DCIEM SUSOPS (sustained operations) battery involving three tasks, each running for 3 min [SRT (serial reaction time) (21), LR (logical reasoning) (1), and SS (serial subtraction) (4) tasks]. The other test battery was a recently developed multitask which ran for 15 min and was designed to simulate the information processing characteristics of flight performance (15,16,20). The task simulates flying an aircraft to specific targets or waypoints. The computer screen shows four separate displays representing four sub-tasks to be performed simultaneously. Three of these four tasks interact. These include vigilance sub-tasks with altitude change commands visible for only 5 s on one display. On another display with two attitude indicators, subjects must be vigilant in order to determine when the two attitude indicators disagree, and then based on flight director parameters, determine which of the attitude indicators accurately reflects the aircraft attitude. A bar task (analagous to managing the power quadrant of a large multi-engine transport) does not interact with the other three sub-tasks. The measures of performance include scores related to error detection and selective attention, visuomotor tracking and coordination, short-term memory, mental arithmetic, and scanning strategies. The raw output data file was merged with a computer reduction algorithm to yield a single final weighted composite score that reconciles correct responses and errors. This task is explained in more detail elsewhere (16,20).

Statistical Analysis

The subjective levels of sleepiness and fatigue as well as the dependent variables (number of correct responses for the SUSOPS tasks and total score for the multitask) from the cognitive tasks were plotted over trials for each of the two 5-wk treatment sessions. The dependent variables from the questionnaires were also plotted over trials. The subjective sleepiness and fatigue data, cognitive data, and the side-effect questionnaire data were submitted to two-factor (2 levels of drugs × 5 levels of weeks) repeated-measures analysis of variance. These analyses of variance were repeated with the addition of gender (male/female) as a between factor in order to compare performance and side effects across gender. In order to assess the impact of increasing dose from week 1 to week 3, all data sets (**Table I** data, psychomotor data from **Fig. 1–4**, and **Table II** data) were run using a modified two-factor (2 levels of drug × 3 levels of weeks) repeated-measures analysis of variance. The Least Significant Difference Test was used to assess planned comparisons. The acceptable level of significance for all main effects or interactions was 0.05.

RESULTS

Subjective Sleepiness and Fatigue

There was a drug × weeks interaction for sleepiness $F(4,72) = 2.82$, $p < 0.03$. Post hoc analysis of this interaction reveals that at week 4, subjects had higher sleepiness scores on sertraline than on placebo, $p < 0.05$. There were no significant main effects or interaction for mental or physical fatigue. The subjective sleepiness and fatigue data are illustrated in Table I.

Psychomotor Data

With respect to serial reaction time performance, there was a main effect of weeks $F(4,72) = 5.90$, $p <$

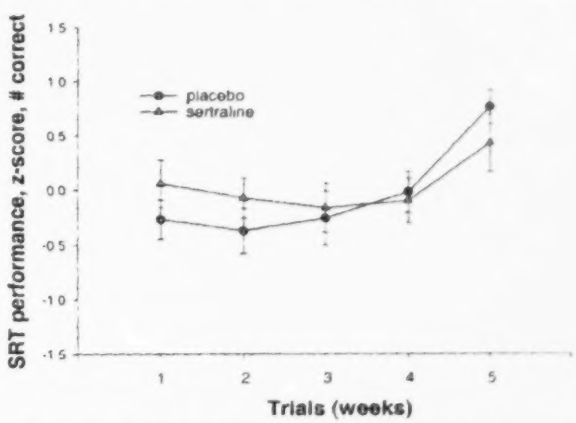

Fig. 1. Serial Reaction Time Task. z-scores for number of correct responses. All values are (Mean ± SEM) and are plotted across drugs and trials.

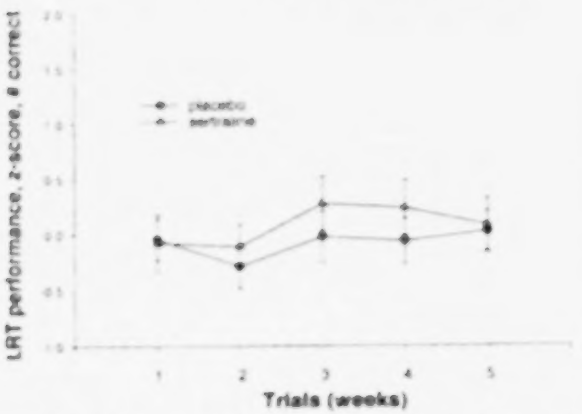

Fig. 2. Logical Reasoning Task. z scores for number of correct responses. All values are (Mean ± SEM) and are plotted across drugs and trials.

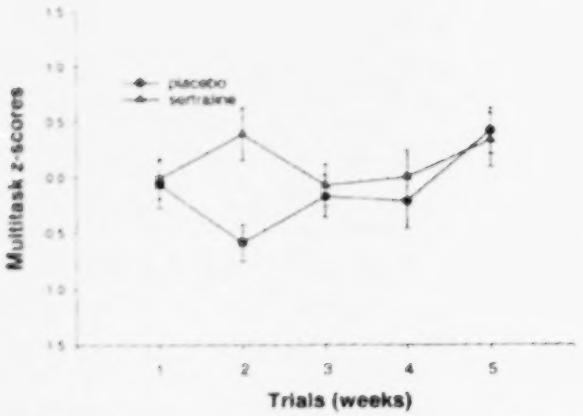

Fig. 4. Multitask "score" z-scores. All values are (Mean ± SEM) and are plotted across drugs and trials.

0.0004 but no effect of sertraline (Fig. 1). Post hoc analysis of the main effect of weeks reveals that at week 5 of both drug arms, performance was better than for weeks 1–4, $p < 0.0007$, $p < 0.0001$, $p < 0.0001$, and $p < 0.001$, respectively. The improvement at week 5 could be because the subjects were happy to be completing a long course of medication and were able to better marshal their cognitive resources. This possibility is consistent with previous findings using this task in our laboratory, where subjects in the process of conducting the last trial of a long study condition can show what might be considered to be a motivation/relief-induced improvement in performance. A completely repeated-measures analysis of variance reduces overall variability by removing between-subject differences from the error term. Note that Fig. 1–4 are graphed with z-scores in order to better demonstrate the within subjects treatment effects. The analyses of variance were equivalent whether done with z-scores or with original units.

There were no significant main effects or interaction in logical reasoning performance (**Fig. 2**). This indicates that there was no impact of sertraline on logical reasoning performance and that performance on this task remained unchanged throughout both 5-wk arms.

There were no main effects or interaction with respect to serial subtraction performance indicating no impact of sertraline on this task (**Fig. 3**). Further, performance on this task remained unchanged throughout both 5-wk arms.

With respect to multitask performance (**Fig. 4**) there were no main effects or interaction. However, given the appearance of a difference in performance (between sertraline and placebo in week 2) the modified analysis of variance was run to assess the effect of increasing dose from week 1 to week 3. This ANOVA yielded a drug × weeks interaction $F(2,36) = 3.09$, $p < 0.052$, and post hoc testing revealed that performance was better on sertraline than on placebo in week 2, $p < 0.002$. In view of this result with the modified ANOVA (3 wk of trials vs. 5 wk of trials), all analyses of variance (Table I data, psychomotor data from Fig. 1–4, and Table II) data were re-run (to assess the impact of increasing dose from weeks 1–3) using the modified ANOVA. The results indicated no further differences relative to the original ANOVA on these data.

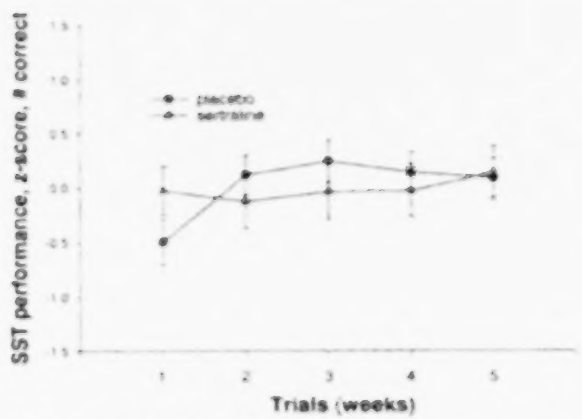

Fig. 3. Serial Subtraction Task. z scores for number of correct responses. All values are (Mean ± SEM) and are plotted across drugs and trials.

Questionnaire Side Effect Data

The questionnaire side-effect data are illustrated in Table II. With respect to insomnia, sertraline was associated with increased difficulty getting to sleep (relative to placebo) $F(1,18) = 12.81$, $p < 0.002$, with an increase in the number of awakenings $F(1,18) = 9.04$, $p < 0.008$, and with increased difficulty returning to sleep after awakening $F(1,18) = 15.12$, $p < 0.001$.

Relative to placebo, sertraline caused more dry mouth $F(1,18) = 7.08$, $p < 0.016$, nausea $F(1,18) = 14.05$, $p < 0.001$, and diarrhea $F(1,18) = 5.90$, $p < 0.026$. Subjects reported more tremors $F(1,18) = 10.07$, $p < 0.005$, and an increase in sweating $F(1,18) = 7.90$, $p < 0.01$.

Further, relative to placebo, sertraline caused a drug × weeks interaction for severity of drowsiness $F(4,72) = 3.46$, $p < 0.012$. Post hoc analysis of this

TABLE II SIDE EFFECT QUESTIONNAIRE SCORES ACROSS WEEKS, FOR PLACEBO AND SERTRALINE. SCORE SCALE RANGED FROM 1 TO 7 WITH HIGHER SCORES INDICATING MORE PRONOUNCED SIDE EFFECTS

	Questionnaire Scores (Mean ± SEM)				
	Week 1	Week 2	Week 3	Week 4	Week 5
Difficulty getting to sleep					
Placebo	1.35 ± 0.17	1.53 ± 0.27	1.41 ± 0.19	1.35 ± 0.17	1.76 ± 0.27
Sertraline	1.95 ± 0.32*	2.26 ± 0.33*	2.26 ± 0.33*	3.00 ± 0.39*	2.44 ± 0.37*
Number of awakenings					
Placebo	0.73 ± 0.26	0.59 ± 0.16	0.56 ± 0.14	0.62 ± 0.15	0.62 ± 0.16
Sertraline	1.02 ± 0.35	1.68 ± 0.32*	1.32 ± 0.27*	1.61 ± 0.29*	1.28 ± 0.29*
Difficulty returning to sleep					
Placebo	1.29 ± 0.15	1.29 ± 0.15	1.24 ± 0.09	1.24 ± 0.12	1.24 ± 0.12
Sertraline	2.47 ± 0.32*	2.21 ± 0.30*	2.11 ± 0.32*	2.28 ± 0.34*	1.94 ± 0.25*
Severity of dry mouth					
Placebo	1.35 ± 0.17	1.65 ± 0.22	1.35 ± 0.19	1.29 ± 0.15	1.41 ± 0.15
Sertraline	1.68 ± 0.25	2.05 ± 0.27	2.32 ± 0.32*	2.28 ± 0.30*	2.17 ± 0.3*
Severity of nausea					
Placebo	1.12 ± 0.07	1.47 ± 0.23	1.29 ± 0.18	1.18 ± 0.08	1.06 ± 0.05
Sertraline	1.89 ± 0.30*	1.84 ± 0.34	1.95 ± 0.25*	2.33 ± 0.35*	1.94 ± 0.26*
Severity of diarrhea					
Placebo	1.24 ± 0.12	1.71 ± 0.20	1.24 ± 0.10	1.24 ± 0.10	1.35 ± 0.15
Sertraline	1.74 ± 0.34	2.21 ± 0.30	2.10 ± 0.28*	2.5 ± 0.33*	2.31 ± 0.26*
Severity of tremors					
Placebo	1.06 ± 0.05	1.0 ± 0.00	1.0 ± 0.00	1.06 ± 0.05	1.06 ± 0.05
Sertraline	1.74 ± 0.34*	1.63 ± 0.30*	1.79 ± 0.28*	1.94 ± 0.32*	1.72 ± 0.26*
Severity of sweating					
Placebo	1.31 ± 0.18	1.38 ± 0.18	1.34 ± 0.19	1.19 ± 0.17	1.19 ± 0.09
Sertraline	1.89 ± 0.32*	1.84 ± 0.27	2.26 ± 0.39*	2.00 ± 0.30*	1.89 ± 0.28*
Severity of drowsiness					
Placebo	2.12 ± 0.31	2.18 ± 0.36	1.94 ± 0.33	1.76 ± 0.21	2.06 ± 0.29
Sertraline	2.47 ± 0.34	3.26 ± 0.38*	3.52 ± 0.38*	3.61 ± 0.36*	3.61 ± 0.44*
Severity of dizziness					
Placebo	1.24 ± 0.12	1.24 ± 0.12	1.24 ± 0.16	1.24 ± 0.12	1.12 ± 0.07
Sertraline	1.47 ± 0.23	1.36 ± 0.14	1.31 ± 0.13	1.50 ± 0.19	1.39 ± 0.19
Level of libido†					
Placebo	3.71 ± 0.17	4.00 ± 0.08	3.82 ± 0.16	3.94 ± 0.16	3.65 ± 0.22
Sertraline	4.03 ± 0.03	3.78 ± 0.12	3.95 ± 0.14	3.50 ± 0.18*	3.72 ± 0.13
Difficulty with ejaculation†					
Placebo	4.09 ± 0.08	4.00 ± 0.00	3.73 ± 0.25	3.82 ± 0.27	3.82 ± 0.27
Sertraline	4.00 ± 0.00	3.91 ± 0.29	4.33 ± 0.41	5.58 ± 0.31*	5.17 ± 0.30*

* Significant difference (see text)
† 4 = normal.

interaction indicates that drowsiness was worse while on sertraline than while on placebo for weeks 2 to 5, ($p < 0.001$, $p < 0.00004$, $p < 0.00001$, and $p < 0.00005$, respectively) but not for week 1. There was no impact of sertraline on dizziness.

With respect to sexual dysfunction there was a drug × trials interaction on the 'level of libido' $F(4,72) = 2.66$, $p < 0.039$ and a drug × trials interaction for "difficulty with ejaculation" $F(4,44) = 7.05$, $p < 0.0002$. Post hoc analysis reveals that "level of libido" was worse on sertraline than on placebo only during week 4 $p < 0.019$ and "difficulty with ejaculation" was worse on sertraline than on placebo only during week 4 ($p < 0.00001$) and week 5 ($p < 0.0001$).

When the "gender" term was added as a between factor in the ANOVAs, no gender differences were detected in any of the data sets (subjective sleepiness/fatigue data, the psychomotor performance data, or the side-effects questionnaire data).

DISCUSSION

In the current study, using our SUSOPS battery we found no effect of sertraline on choice reaction time, logical reasoning, and serial subtraction performance. Further, we found no effect of sertraline on the multitask (Fig. 4) which assesses aviation relevant performance including scores related to error detection and selective attention, visuo-motor tracking and co-ordination, short-term memory, mental arithmetic, and scanning strategies. The modified ANOVA assessed the impact of changing dose (weeks 1 to 3) and revealed what might be a sertraline-induced increase in multitask performance, relative to placebo performance, in week 2. Such a result would be consistent with previous work indicating that sertraline has been found to facilitate improvement in cognitive/psychomotor performance (2,6–8,13). This improvement in week 2 could indicate that the 100 mg dose of sertraline (week 2) improves multitask performance while the 50 mg dose (week 1) and the 150 mg dose (weeks 3–5) do not. However, Fig. 4 suggests that the effect is due as much to a decrease in performance while on placebo as it is due an increase in performance while on sertraline. This suggests that the transient improvement in week 2 multitask performance may be an artifact.

Our questionnaire data confirm previously known

side effects. We found that sertraline causes initial insomnia (difficulty getting to sleep), a slightly increased number of awakenings, and middle insomnia (difficulty returning to sleep after awakening) as well as an increase in somnolence (drowsiness) which was only manifested after week 1. This delayed increase in drowsiness is perhaps due to a dose-response effect given that in the first week the subjects only received a daily 50 mg dose of sertraline which increased to 100 mg in the second week, and 150 mg daily throughout the remaining 3 wk.

Curiously, this drowsiness is not evident in the sleepiness data. The results of this study indicate that our subjects experienced a transient subjective increase in sleepiness (Stanford Sleepiness Scale) relative to placebo while on sertraline during week 4 only. Nevertheless, perhaps a long-term study needs to be undertaken in order to clarify whether or not sertraline-induced drowsiness is transient, and if not, whether or not it effects psychomotor performance over the longer term.

Sertraline also affected the gastro-intestinal system by increasing nausea and diarrhea, as well as the autonomic system by causing an increase in dry mouth and in sweating.

SSRIs have been shown to cause sexual dysfunction ranging from decreased libido and decreased arousal to delayed orgasm, but the precise incidence is unknown (19). Sertraline has significantly decreased reported levels of libido, arousal, and duration of orgasm; significantly increased time to arousal; and produced a trend toward a decrease in orgasm intensity (14). In our study, the small impact of sertraline on libido was only evident during week 4 with libido returning to placebo levels during week 5. Difficulty with ejaculation was only manifest during weeks 4 and 5. This difficulty might have been evident earlier if the subjects had been taking the full 150 mg dose at the beginning of the treatment.

A syndrome of apathy or lethargy (serotonin syndrome) is sometimes associated with the use of SSRIs (11,19). We did not find any evidence of serotonin syndrome in our subjects.

The small sertraline-induced increase in tremors reflects an effect on the peripheral nervous system. This subjective report of tremors did not have an objective effect on the measures of performance. There was no impact on the central nervous system as quantified by dizziness ratings. An increase in dizziness might make pilots more prone to vertigo and could be considered a potential flight safety problem.

Unfortunately, the statistical power in our study was low because the performance distributions for placebo and sertraline conditions were very similar and because we were able to recruit only 20 subjects. Therefore, the possibility of a type II error cannot be ruled out. Nevertheless, the results of our study are consistent with earlier work which indicates that sertraline in normal subjects either has no impact on psychomotor performance (11), or improves it in spite of subjective reports of side effects, especially drowsiness (2,6–8) and sleep difficulties (2). With respect to the question of whether or not our findings can be extrapolated to include depressed pilots who have been treated, we believe that pilots whose depression is in remission should not be effected by depression and should therefore behave "normally." Therefore, it is reasonable to conduct studies to determine the possible impact of sertraline (or other anti-depressants) by using normal healthy subjects, which of course are much more abundant/readily available than depressed subjects.

CONCLUSIONS

The current study found no impact of sertraline on traditional psychomotor tests nor on a complex battery simulating flying performance. Study subjects subjectively experienced a number of known sertraline side effects including insomnia, drowsiness, and tremor. Although these subjective side effects did not translate into measurable performance effects, they are of potential concern when considering a return to flying duties while taking sertraline.

There is a growing interest in the possibility of returning to restricted flying duties aircrew who are being treated for depression with sertraline or other SSRIs once all symptoms of depression have resolved and maintenance treatment continues. This study provides information on the absence of sertraline effects on psychomotor performance in non-depressed subjects. These findings support the possibility of selected use in aircrew and should be helpful in the ongoing aeromedical discussion about this evolving issue (10).

ACKNOWLEDGMENTS

We are indebted to Dr. Ross Pigeau for statistical consultation and for reviewing this manuscript.

REFERENCES

1. Baddley AD. A 3 min reasoning test based on grammatical transformation. Psychonomic Sci 1968; 10:341–2.
2. Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of effective disorders-III. tolerability, safety and pharmacoeconomics. J Psychopharmacol 1998; 12(3, Suppl B):S55–87.
3. Harris DA, Pegram FV, Hartman BO. Performance and fatigue in experimental double-crew transport missions. Aviat Space Environ Med 1971; 24:980–6.
4. Heslegrave RJ, Angus RG. The effects of task duration and work-session location on performance degradation induced by sleep loss and sustained cognitive work. Behav Res Methods Inst Comp 1985; 17:592–603.
5. Hindmarch I. The behavioural toxicity of the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 1995; 9(Suppl 4):13–7.
6. Hindmarch I, Bhatti J. Psychopharmacological effects of sertraline in normal, healthy volunteers. Eur J Clin Pharmacol 1988; 35:221–3.
7. Hindmarch I, Kimber S, Cockle SM. Abrupt and brief discontinuation of antidepressant treatment: effects on cognitive function and psychomotor performance. Int Clin Psychopharmacol 2000; 15:305–18.
8. Hindmarch I, Shillingford J, Shillingford C. The effects of sertraline on psychomotor performance in elderly volunteers. J Clin Psychiatry 1990; 51(8, Suppl B):34–6.
9. Hoddes E, Zarcone V, Smythe H, et al. Quantification of sleepiness: a new approach. Psychophysiology 1973; 10:431–36.
10. Ireland R. Pharmacologic considerations for seratonin reuptake inhibitor use by aviators. Aviat Space Environ Med 2002; 73:421–9.
11. Lane R, Baldwin D. Selective serotonin reuptake inhibitor in-

duced serotonin symbdrome: review. J Clin Psychompharmacol 1997; 17:208–21.
12. Lipinski JF Jr, Mallya G, Zimmerman P, Pope HG Jr. Fluoxetine-induced akathisia: clinical and theoretical implications. J Clin Psychiatry 1989, 50 339–42.
13. Mattila MJ, Saarialho-Kere U, Mattila M. Acute effects of sertraline, amitryptyline, and placebo on the psychomotor performance of healthy subjects over 50 years of age. J Clin Psychiatry 1988; 49(8, Suppl):52–8.
14. Modell JG, Katholi CR, Modell JD, DePalma RL. Comparative sexual side effects of bupropnion, fluxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997, 61:476–87.
15. Paul MA, Brown GM, Buguet A, et al. Melatonin, and zopiclone as pharmacologic aids to facilitate crew rest. Aviat Space Environ Med 2001, 72 974–84.
16. Paul MA, Pigeau RA, Weinberg H. CC130 pilot fatigue during re-supply missions to former Yugoslavia. Aviat Space Environ Med 2001; 72 965–73.
17. Petty F, Davis LL, Kabel D, Kramer GL. Serotonin dysfunction disorders. A behavioural neurochemistry perspective. J Clin Psychiatry 1996; 57(suppl 8):11–6.
18. Settle EC. Antidepressant drugs: disturbing and potentially dangerous adverse effects. J Clin Psychiatry 1998; 59(Suppl 16): 25–30.
19. Settle EC. Buproprion: a novel antidepressant: update 1989. International Drug Therapy Newsletter 1989, 24(8) 29–36.
20. Weinberg H, Jantzen KJ, Cheyne D, et al. Jetlag, gamma activity, and managing pilot fatigue. In: Posluns H, ed. Transport Canada Conference Proceedings TP 13375. Fatigue in Transportation Workshop: Multimodal Issues and Solutions, October 15–16, 1998. Ottawa: Transport Canada, 1998.
21. Wilkinson RT, Houghton D. Portable four-choice reaction time test with magnetic tape memory. Behav Res Methods Inst Comp 1975, 7:441–6.
22. Winokur A, Lexow NJ, Allen K, et al. Sertraline administered for 8 weeks to depressed patients did not alter sleep architecture: a preliminary report. New Research Program and Abstracts. American Psychiatry Association Annual Meeting, 1994, Philadelphia. Washington, DC: APA.
23. Zawertailo LA, Busto U, Kaplan HL, Sellers EM. Comparative abuse liability of sertraline, alprazolam, and destroamphetamine in humans. J Clin Psychopharmacol 1995; 15.117–24.